REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action with appreciation. Claims 14-26 remain pending in the application; however, Claims 15-22 and 24 remain withdrawn from consideration as a result of the previously issued Restriction Requirement. The Office maintains a rejection under 35 USC § 102 and raises new rejections under 35 USC § 102 and 35 USC § 103. The Office maintains the obviousness-type double patenting rejection (in part) and also raises an objection as to form.

The Office acknowledges the priority claim to French Application FR 00.08793 but states that a certified copy of the priority document has not been received by the Office. With the instant Response, the Applicants submit a certified copy of the French priority document (French Application FR 00.08793, filed July 6, 2000) and a certified translation thereof into English, thereby perfecting the claim to priority under 35 USC § 119, which claim was made upon filing.

Claims 23 and 25-26 are rejected for lack of enablement under 35 USC § 112, first paragraph. It is the position of the Office that one skilled in the art would recognize that the process of preparing any pharmaceutical composition will produce ***the*** thermodynamically stable crystalline form. Therefore, the Office concludes that "the instant α-crystalline [form], after mixing, grinding, compressing would be transformed into a thermodynamically stable form(s)." The Office cites the Brittain reference to support this allegation. The Office goes on to state that there is no data in the specification which demonstrate that the instant α-crystalline form is present in the instant pharmaceutical compositions.

The Applicants respectfully submit that the Brittain reference also states that "[a]s tableting speeds increase towards commercial production, exposure times to stress decrease and one would anticipate even less chance for crystalline conversion. For the production of many substances, this situation is certainly true." The reference goes on to describe a study involving thirty-two (32) drugs *known to exist in different polymorphic states*. Of these thirty-two (32) drugs, eleven (11) appear to have been designated "transforming substances," and of these eleven (11) substances,

detailed studies of tableting were conducted on only three (3) substances. The reference also discloses additional studies done on crystalline forms of other drugs as well as studies done on drugs containing amorphous material.

Thus, the Applicants respectfully submit that the data for specific compounds (which are structurally unrelated to the instantly claimed α-crystalline form of perindopril t-butylamine salt) disclosed in the cited reference may not be extrapolated to the instant α-crystalline form of perindopril t-butylamine salt, and that such data does not support the generalized speculation of the Office with respect to pharmaceutical compositions comprising polymorphs.

Moreover, with the instant Amendment, Claim 23 has been amended to recite a solid pharmaceutical composition.

Thus, the Applicants respectfully submit that the instant pharmaceutical compositions are enabled by the disclosure in the instant specification. Reconsideration and withdrawal of the lack of enablement rejection is respectfully requested.

Claims 25 and 26 remain rejected under 35 USC § 102(e) as being anticipated by Guez, et al. (US Patent No. 6,653,336). It is the position of the Office that Guez, et al. disclose a pharmaceutical composition tablet comprising perindopril t-butylamine salt and a diuretic, such as indapamide, and that the disclosed pharmaceutical composition anticipates the instant pharmaceutical composition comprising the instant α-crystalline form of perindopril t-butylamine salt and a diuretic, including indapamide.

The Office states that the only difference between the instant claims and the cited references is that the Guez, et al. references are silent with respect to X-ray diffraction data. The Office goes on to state that, according to MPEP § 2112, "something which is old does not become patentable upon the discovery of a new property." Thus, the Office maintains its assumption that the X-ray diffraction data associated with instant α-crystalline form of perindopril t-butylamine salt is an

inherent property of the "perindopril t-butylamine salt" disclosed in the Guez, et al. references.

The Applicants respectfully submit that MPEP § 2112 also states that "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient' " and that "the fact that a certain result or characteristic may occur or be present in the prior art is not enough to establish the inherency of that result or characteristic." Thus, the Applicants respectfully reiterate that Guez, et al. do not disclose that the perindopril t-butylamine salt used in the disclosed pharmaceutical compositions is in ***any*** crystalline form, much less in the instant α-crystalline form, and that the Office has not demonstrated that the "allegedly inherent characteristic" ***necessarily flows from the teaching of the cited reference***. Recognition of the Office procedure in this regard and withdrawal of the rejection are respectfully solicited.

Claims 23 and 25-26 are also now rejected under 35 USC § 102(b) as being anticipated by the equivalent Guez, et al. PCT International Application PCT/FR98/00411 (published as WO 99/25374). It is the position of the Office that Guez, et al. disclose a pharmaceutical composition comprising perindopril t-butylamine salt which may be in the form of an injectable preparation or an aqueous solution. The Office goes on to state that, in an aqueous solution, the instant α-crystalline form would exist in "free form" and not "crystal form" and that, therefore, an aqueous pharmaceutical composition comprising the instant α-crystalline form is anticipated by the disclosure of Guez, et al.

The Applicants respectfully submit that the amended claims, directed to solid pharmaceutical compositions, are not anticipated by the Guez, et al. disclosure of injectable preparations and/or aqueous solutions.

Reconsideration and withdrawal of the rejections under 35 USC § 102 is respectfully requested.

Claims 14, 23, and 25-26 are further rejected for obviousness under 35 USC § 103(a) based on Guez, et al. (WO 99/25374). It is the position of the Office that, Guez, et al. disclose perindopril t-butylamine salt and pharmaceutical compositions comprising perindopril t-butylamine salt, including pharmaceutical compositions which further comprise a diuretic, such as indapamide, and that it would have been obvious to one skilled in the art to employ the compounds/compositions of Guez, et al. to obtain the instant α-crystalline form of perindopril t-butylamine salt and its pharmaceutical compositions.

The Office also states (at page 10 of the instant Office Action, citing In re Cofer, 148 USPQ 268 (CCPA)) that "...changing the form purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity, or characteristic was inherent in or rendered obvious by the prior art."

As noted above with respect to the anticipation rejection, the Applicants respectfully submit that MPEP § 2112 states that "the fact that a certain result or characteristic may occur or be present in the prior art is not enough to establish the inherency of that result or characteristic."

The Applicants respectfully reiterate that there is no disclosure in the Guez, et al. reference which would suggest to one skilled in the art that the conditions which are disclosed and claimed in the present application, rather than any other possible conditions, would produce the instant α-crystalline form. The selection of the particular conditions for the isolation of the instant crystalline form would require extensive experimentation through trial and error.

As disclosed in the instant specification, as well as in the previously submitted COQUEREL Declaration, the instant α-crystalline form provides the tert-butylamine salt of perindopril in a form that is sufficiently stable to allow it to be stored for a prolonged period, that is perfectly reproducible and that is easily formulated.

Moreover, the Applicants respectfully submit that, in the CCPA decision (In re Cofer) cited in the instant Office Action at page 10, the CCPA held that

> [W]hether a given chemical compound or composition has the same usefulness as closely related materials may be an important consideration in determining obviousness under 35 USC 103. But it is only one consideration. We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the "subject matter as a whole" to be compared with prior art as are other properties of the material which make it useful.

Therefore, notwithstanding the instant demonstration of the superior and unexpected properties associated with the instant α-crystalline form provided in the instant specification and in the previously submitted COQUEREL Declaration, the Applicants further submit that the Office has not made the required demonstration, i.e., that the cited references teach or suggest "the particular structure or form" of the instant α-crystalline form as well as "suitable methods of obtaining that structure or form" to establish a case of *prima facie* obviousness per the CCPA holding of record.

Finally, the Applicants respectfully submit that in a USPTO presentation (available at http://www.cabic.com/bcp/061306/CLow_PPP.ppt and also enclosed with this Response) given on June 13, 2006, Examiner Christopher LOW presented the current USPTO view on polymorphs. This presentation suggests that the current Office position is that a particular polymorph is unobvious based on the unpredictability of its existence and identification.

Thus, the Applicants respectfully submit that the instant α-crystalline form as well as the instant pharmaceutical compositions comprising the α-crystalline form are not

rendered obvious by the disclosure of the Guez, et al. reference. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

The previously issued obviousness-type double patenting rejection of Claim 14 based on co-pending application US Serial No. 11/052,489 has been withdrawn; however, Claims 23 and 25-26 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 9, and 11-12 of this co-pending application. It is the position of the Office that one skilled in the art would recognize that the process of preparing any pharmaceutical composition will produce the thermodynamically stable crystalline form and that, therefore, the β-crystalline form claimed in the US Serial No. 11/052,489 and the instant α-crystalline form would be transformed into the same thermodynamically stable form during the process of preparing a pharmaceutical composition. The Office again cites the Brittain reference to support this allegation.

As noted above with respect to the lack of enablement rejection, the Applicants respectfully submit that the Brittain reference does not support the generalized speculation of the Office with respect to pharmaceutical compositions comprising polymorphs.

Moreover, the Applicants respectfully submit that there is nothing in co-pending application US Serial No. 11/052,489 to suggest pharmaceutical compositions comprising the particular α-crystalline form. Thus, the instant pharmaceutical compsitions, comprising the α-crystalline form of perindopril t-butylamine salt, are patentably distinct from the limited disclosure of pharmaceutical compositions comprising the β-crystalline form of perindopril t-butylamine salt. Reconsideration and withdrawal of the obviousness-type double-patenting rejection is respectfully requested.

Finally, the Applicants request rejoinder of dependent species and method claims upon the identification of a patentable genus.

* * * * *

Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: 

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Enclosure: Certified Copy of French Priority Application FR 00.08793 and Certified Translation thereof into English; Listing of Claims; and Postal Card Receipt

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THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

Biotechnology/Chemical/Pharmaceutical Customer Partnership

June 13, 2006 Meeting
Madison Building Auditorium

United States Patent and Trademark Office
Alexandria, Virginia
600 Dulany Street, Alexandria, VA,

Driving & Metro Directions /Hotels (Word) Campus Map (html) Campus Map (Power Point)

Morning Session

	Greetings and Overview Greetings 7 slides 2.95M TC1600 - Organization Chart 1 page Excel 48K	John LeGuyader, Bruce Kisliuk, George Elliott, Directors, Technology Center 1600
9:15-10:00 AM	International Cooperative Projects 4 slides 13K	Mark Powell Director, Technology Center 2600
10:00 –10:15 AM	Break	
10:15 – 11:00 AM	Restriction Reform and TC1600 Restriction Practice Action Plan 22 slides 134K	Kathleen Fonda, Office Patent Legal Administration
11:00 - 11:45 AM	SCORE (Supplemental Complex Repository for Examiners) 32 slides 3.7M	Lisa Hobbs, SIRA
11:45 – 1:00 PM	Lunch Roundhouse Cafe Cafeteria is inside Madison Building lower level. Menu for the Week in PDF is here	

Afternoon Session

1:00 – 1:45 PM	Nanotech Update 26 slides 2.3M	Dave Nguyen, Supervisory Patent Examiner, Art Unit 1633
1:45 – 2:30 PM	Polymorphs in Pharmaceutical Products 18 slides 44K	Christopher Low, tQAS TC 1600
2:30 – 2:45 PM	Break	
2:45-3:30	Examination of Stem Cell Practice 22 slides 157K	Deborah Reynolds, tQAS, TC1600
3:30 – 3:45 PM	Closing Remarks/Discussion	John LeGuyader, Bruce Kisliuk, George Elliott,

Polymorphs in Pharmaceutical Products

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Definition Of Polymorphs

- Polymorphs are different crystalline forms of the same pure substance in which molecules have different arrangements and/or different molecular conformation.

Definition Of Polymorphs (contd)

- Polymorphic solids have different unit cells.
- Display different physical properties such as unit packing, thermodynamic, spectroscopic, interfacial, and mechanical properties.

Physical Properties Differ Among Various Polymorphs

- Molar volume and density
- Refractive index
- Melting and sublimation temperatures
- Enthalpy (i.e., heat content)
- Solubility
- Vibration transitions (i.e., infrared absorption spectra and Raman spectra)

Physical Properties Differ Among Various Polymorphs (contd)

- Dissolution rate
- Stability
- Hardness
- Compatibility
- Handling, flow, and blending

Polymorphs

- An amorphous form is not a polymorph
- A clathrate or a hydrate can be a polymorph

Amorphous Forms

- Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties are sometimes regarded as a polymorph.
- Unlike true polymorphs, an amorphous form is not a single type of crystal and not considered a polymorph.

Clathrate/Inclusion Compounds

- A chemical substance consisting of a lattice of one type of crystal structure trapping and containing a second type of molecule. Therefore, a clathrate is a material which is a weak composite, in which molecules of suitable size are captured in spaces which are left by the other compounds.
- Molecules of one substance are completely enclosed within the crystal structure of another.

Channel Hydrates Compound.xH_2O

- Hydrates in this class contain water in lattice channels, where the water molecules included lie next to other water molecules of adjoining unit cells along an axis of the lattice forming "channels" through the crystal.

Claiming A Polymorph

- Include name or structure of the chemical compound.
- Apply a "standard" convention to designate and name the polymorphic form and distinguish it from other polymorphic and pseudomorphic forms already in the art.
- Incorporate comparison and characterization data.

Structure of three compounds

- Cpd.HCl
- Cpd.H_2O
- Cpd.HCl.H_2O, a new compound

Polymorphs May Be Unobvious Over Prior Art Forms

- The specific crystal lattice(s) and number of lattices of a polymorph are not predictable.
- Even if one could predict that polymorphs exist, there is no general teaching or suggestion in the art that allows one to predict how to make a particular polymorph.
- No teaching or suggestion exists in the art to identify and to appreciate the properties and characteristics of a particular polymorph prior to it being identified.

Polymorphs May Be Unobvious Over Prior Art Forms (contd)

- A method of making the new polymorph was not known until its identification.
- The new crystalline form has different properties over the prior art compound.

Polymorphs May Be Unobvious Over Prior Art Forms (contd)

- It may not be obvious, and not possible to predict
  - How many different crystal forms can be prepared
  - How to prepare any, as yet unknown, crystal forms
  - The properties of any, as yet unknown, crystal forms

  Therefore, new crystal forms are potentially patentable entities

Include Available Polymorph Comparison and Characterization Data Such As:

XRPD
Single crystal x-ray
Infrared absorption
Raman spectroscopy
Solid state NMR
Morphology determination

Include All Available Polymorph Characterization Data Such As: (contd)

- Beyond having a diverse collection of characterization data, the data for a novel polymorph should be analyzed to demonstrate how it distinguishes over other disclosures including the compound per se, and more particularly, over other polymorphic forms.

Include all available polymorph characterization data such as (contd)

- Furthermore, characterization data that evidences unexpected or superior properties over properties of the compound per se, and other polymorphic forms, could make the prosecution easier.

QUESTIONS